Nitrites in the Treatment of Bronchial Asthma*

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Spasm of the smooth muscle of the bronchi and bronchiole, edema of the mucosa leading to mucous collection, and occlusion of alveoli probably cause most of the symptoms of asthma. This resultant bronchial inflammation and obstructive emphysema may be acute, recurrent, or chronic. The degree to which these changes interfere with the passage of respiratory gases determined the severity of the condition. Frequently, one is unable to uncover the causative factors of these anatomic and physiologic changes. Many times, even when the causes are known, the difficulty of eradicating these factors has made symptomatic therapy the standby for the treatment of bronchial asthma.

For many years, the sympathomimetic drugs have been the foundation upon which the majority of bronchial asthmatic remedies have been built. Epinephrine was modified to form isopropylnoradrenalin in the search for drugs with greater ease of administration, prolongation of

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effect and milder side reactions. Ephedrine was also employed for this purpose. The xanthines came into use because of their ability to relieve smooth muscle spasm. All of these drugs are effective in various degrees, but resistance develops to each and side effects may limit the quantities used. One attempt to overcome the resistance that the patient develops to the sympathomimetic drugs was the utilization of the drugs in combination with ganglionic blocking agents.\(^1\) This is of some help, but the

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Pre-Med</th>
<th>10 Min.</th>
<th>20 Min.</th>
<th>45 Min.</th>
<th>60 Min.</th>
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<td>W</td>
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<td>C</td>
<td>56</td>
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<td>63</td>
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<td>33</td>
<td>M</td>
<td>W</td>
<td>56</td>
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<td>54</td>
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<td>F</td>
<td>C</td>
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<td>54</td>
<td>60</td>
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<td>C</td>
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<tr>
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<td>C</td>
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<td>Y. B.</td>
<td>27</td>
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<td>C</td>
<td>50</td>
<td>52</td>
<td>40</td>
<td>60</td>
<td>—</td>
<td>—</td>
<td>Cooperation poor</td>
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\(^1\) This is of some help, but the

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TABLE 1 — 1 SECOND TIMED VITAL CAPACITY
0.8 Mg. NITROGLYCERINE-SUBLINGUAL
(Per cent)
potency of the ganglionic blocking agent used is limited by the undesirable side effects or rather extension of action of the drugs. Steroids have been used during the past decade, but here again, dangerous side effects appear with increased dosage and/or prolonged administration. An additional problem is the reexacerbation of the disorder if withdrawal of the drug is too abrupt. Expense of the medication may at times be a problem. Meperidine hydrochloride is resorted to by Segal when other measures fail or fastness to epinephrine or to the xanthines has developed. This cannot be recommended as a routine measure, however, and too large or too frequent a dose may depress respiration.

Ideally, bronchodilation should be the only effect of a drug used for the symptomatic relief of bronchial asthma. Bronchodilatation leads to an increased rate and depth of respiration. Oxygen intake is augmented, and the level of oxygen consumption of the tissue cells elevated, producing greater tissue oxygenation. The relaxing action of the nitrates on smooth muscle was recognized and exploited to effect bronchiole dilatation early in the modern era of medicine. In addition to sublingual
administration, early methods included the inhalation of the fumes produced by the burning of potassium nitrite combined with stramonium, and by burning paper impregnated with saltpeter. Both of the remedies caused the reduction of nitrate to nitrite in the fumes to be inhaled. Ease of administration was certainly not one of the virtues of such means of medication. About the end of the first decade of this century these drugs gradually lost favor and fell into disuse.

Johnson et al., noting the effectiveness of sublingual nitroglycerine in the relief of the respiratory distress of paroxysmal nocturnal dyspnea, attempted to determine the response of the drug on pulmonary artery pressures in patients with failure of the left ventricle. In a physiologic study using right heart catheterization, nitroglycerine was shown to produce a prompt reduction in the pulmonary artery hypertension associated with failure of the left ventricle.

When we applied these results clinically to patients in varying degrees of congestive failures, it was observed that the cases of cor pulmonale associated with chronic bronchial asthma had the greatest relief of respiratory distress when treated with nitroglycerine. It was postulated that the nitrite had a two-fold action both in reducing the pulmonary artery hypertension and relieving the concomitant bronchial spasm. Utilizing plethysmographic methods for evaluating nitrites used in the treatment of cardiovascular disease, we found that nitroglycerine
and erythrol tetranitrate were as effective orally as sublingually in potency and duration of their vasodilating effect. Onset of action was little affected by the different modes of administration.

With these observations in mind, it was thought feasible to conduct a study of the effects of nitroglycerine as a short acting nitrite, and erythrol tetranitrate as a long acting nitrite, upon patients with bronchial asthma. Isopropylarterenol was also included in the evaluation, since it is a widely used and accepted epinephrine derivative, and in that capacity might serve as a yardstick against which to compare the therapeutic effectiveness of the nitrites.
Method

The purposes of testing pulmonary function in bronchial asthma are to determine the degree of disability of the patient, to follow the progress of the disease in individual cases, to provide a means of direct testing of the pulmonary tree with suspected allergens, and to assay the effectiveness of various therapeutic drugs.\textsuperscript{18}

The tests of pulmonary function employed in bronchial asthma include the vital capacity, timed vital capacity and index of intrapulmonary mixing of gases as determined by the open circuit or closed circuit method.

The vital capacity is the maximal volume of gas that can be expired from the lungs by forcible effort after a maximal inspiration. It may be normal or decreased in patients with bronchial asthma as compared with the predicted normal.\textsuperscript{11} Cournand\textsuperscript{11} described a method of graphic registration of breathing by means of a modified basal metabolism apparatus and noted that change in the form of deep breathing, particularly retarded expiration, revealed early stages of pulmonary emphysema or bronchial asthma. Gaensler\textsuperscript{13} found that timed vital capacity measurements provide a method for indicating marked slowing of the expiratory phase commonly found in both these conditions. In the presence of airway obstruction or impaired elastic recoil, small reductions of total vital capacity are accompanied by marked decrease of timed capacities. Unlike the vital capacity, the time capacities correlate well with maximal breathing capacity, air velocity index, and the ratio of residual volume to total lung capacity.

![Graph showing 1 second timed vital capacity over time in minutes for nitroglycerine and isuprel](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21352/)
The maximal breathing capacity is not a practical method when one is desirous of evaluating the onset and duration of action of a drug since it is a tiring procedure and therefore cannot be repeated at closely spaced intervals. It is an excellent method when employed to gauge the long term response of a patient to a drug and was thusly employed in our study. To determine the onset, maximum response and duration of action of the drugs used in this study, we employed closed circuit spirometry for graphic recordings when it was feasible to bring the patient to the apparatus. When it was easier to bring the apparatus to the patient, we used a simple attachment to the ordinary dial type vital capacity machine* which automatically records the total vital capacity and the fraction of the total volume exhaled during the first second of the maximal expiratory effort. Normal persons are capable of exhaling 83, 94 and 97 per cent of the total vital capacity during one, two and three seconds.

**Results**

Nitroglycerine 0.6 mg. was administered sublingually to 11 patients during acute episodes of bronchial asthma. Three of these were unresponsive to intravenous aminophylline 0.5 gm. given one and a half hours prior to nitrite therapy. Their ages ranged from 26 to 52 years, eight women and three men. One second timed vital capacities were recorded by means of a simple timing attachment to the ordinary dial type vital capacity machine prior to medication and 10, 20, 45, 60 and 90 minutes following. In all cases except one, who refused to perform the function tests, there was improvement in the one second vital capacity. All 11 patients showed subjective improvement. (Table 1)

Three patients with bronchial asthma varying from six to 18 years were given erythrol tetranitrate* 15 mg. sublingually and tested by the same method. A one second timed vital capacity was performed prior to medication and 10, 20, 45, and 60 minutes following. They were then placed on a regimen of erythrol tetranitrate 15 mg. orally three times a day for six days. Increased timed vital capacity and subjective improvement was noted in all. (Table 2)

Two patients were given nitroglycerine 0.6 mg. sublingually and the one second vital capacities were recorded by closed method spirometry. This was later repeated with orally administered nitroglycerine. These results (Table 3) indicate that the two methods of administration have equal therapeutic value.

A 51 year-old white man with old pulmonary tuberculosis was referred to us for pulmonary function tests. It was found that his predicted maximal breathing capacity was 47 per cent of normal. He was placed on a regimen of breathing exercises for

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**TABLE 4**

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Date</th>
<th>8-20-58</th>
<th>10-2-58</th>
<th>10-27-58</th>
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<td>Vital Capacity — Total</td>
<td>2472 cc.</td>
<td>2400 cc.</td>
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<td>Per cent Predicted</td>
<td>67</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Second V. C. — Per cent</td>
<td>45</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. B. C. Litters/Min.</td>
<td>44</td>
<td>50</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Per cent Predicted</td>
<td>47</td>
<td>50</td>
<td>67.6</td>
<td></td>
</tr>
</tbody>
</table>

*Supplied as Cardilate®, Burroughs Wellcome and Company, Inc., Tuckahoe, New York.
a one month period. At the end of this time his predicted breathing capacity had increased to 52 per cent of normal. He was then given erythrol tetrannitate 15 mg. three times a day orally for six days. Following this course of therapy his predicted maximal breathing capacity increased to 67.6 per cent of normal. (Table 4) Lobectomy was then successfully performed.

Six patients were evaluated with erythrol tetrannitate 15 mg., nitroglycerine 0.3 mg., and Isuprel 15 mg. by closed spirometry methods and the one second timed vital capacities determined from the graphic recordings. Figures 1 to 6 illustrate the results in each patient. Time of onset of action usually began within 10 minutes with all three drugs. The maximum effect averaged 20 minutes for nitroglycerine and Isuprel and 45 minutes for erythrol tetrannitate. Duration of action was longest for erythrol tetrannitate. (Table 5)

Discussion

The ideal drug for the symptomatic relief of bronchial asthma should have the attributes of ease of administration, potency of action, duration of effect, absence of untoward reaction, economy and the failure to build resistance to the medication. Our results with nitroglycerine and erythrol tetrannitate indicate that oral administration is feasible. The potency of the nitrites used in this study compare favorably with isopropylarterenol (Isuprel), an accepted epinephrine derivative used in the treatment of bronchial asthma. Duration of effect is definitely superior for erythrol tetrannitate. Undesirable side effect of the nitrites are minimal and have been known and studied for years. Resistance to nitrites as used for angina pectoris has never been much of a therapeutic bulwark. We believe that this investigation indicates a place for the nitrites in the armamentarium of drugs used to treat bronchial asthma.

We have used these nitrites on a limited scale for the treatment of congestive heart disease because of their smooth muscle relaxing effect and their ability to lower pulmonary arterial pressure. Our results to date are gratifying enough to indicate the desirability of an expanded investigation into this field.

SUMMARY

1. Nitroglycerine and erythrol tetrannitate are effective drugs for the symptomatic treatment of bronchial asthma.
2. The potency and duration of action of these nitrites surpass that of isopropylarterenol.
3. Sublingual administration has no advantage over oral administration.

RESUMEN

1. La nitroglicerina y el tetrannitato de eritrol son efectivas para el tratamiento sintomático del asma bronquial.
2. La potencia y la duración de acción de estos nitritos sobrepasa la del isopropylarterenol.
3. La administración sublingual no tiene ventajas sobre la administración oral.

RESUMÉ

1. La nitroglycérine et le tetrannitrate d'érythrol sont des produits efficaces dans le traitement symptomatique de l'asthme bronchique.
2. La puissance et la durée d'action de ces nitrates surpassent celle de l'iso-propylarterenol.
3. L'administration sublinguale n'a aucun avantage sur l'administration buccale.
ZUSAMMENFASSUNG

1. Nitroglycerin und Erythol-Tetranitrat sind wirksame Arzneimittel für die symptomatische Behandlung des Bronchial-asthma
3. Gegenüber der oralen Anwendung bietet die sublinguale keine Vorteile.

REFERENCES


ANGIOPNEUMOGRAPHY IN SOME PULMONARY AND MEDIASTINAL DISEASES

Angiopneumography was used in 60 patients affected by lung cancer, various chronic inflammatory lung processes and some mediastinal diseases. In addition, vessel injection of 20 lung preparations removed because of the aforementioned diseases has been made. In lung cancer, angiopneumography reveals poor or no vascularization in the pathologic area. The technic of selective angiopneumography is the best to reveal vascular changes. Angiopneumography was found to be of value in determining signs of inoperable lung cancer.

In chronic lung atrophy, angiopneumography is of no diagnostic value and aids but little in the differential diagnosis of malignant pulmonary growths.

In unresolved pneumonias, there is normal or increased vascularization. Angiography helps to make diagnosis of the aneurysm of mediastinal vessels.


PROPHYLACTIC ACTION OF INH AGAINST WHOOPING COUGH

The authors have observed that INH exerted evident prophylactic influence in respect to whooping cough during an epidemic in a group of children who were given this drug for the prevention of tuberculosis.